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09/148,234	09/04/1998	IOANNIS MOUTSATSOS	GI5298A	3002

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	33

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/148,234	Applicant(s) Moutsatos et al.
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 6, 2003*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11, 12, 14-17, and 19-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11, 12, 14-17, and 19-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *33*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 6, 2003 has been entered.

Status of the Claims

2. The rejection of claims 11, 12, 14-17, and 19-23 under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,763,416 (of record) or WO 96/39431 (of record) in view of US Pat No. 5,645,084 (of record), US Pat No. 5,700,774 (of record) and US 6,048,964 is withdrawn in view of the new grounds for rejection below.

3. Claims 11, 12, 14-17 and 19-23 are pending.

4. New Grounds for rejection are presented below. Response to arguments made in Paper No. 30, filed March 6, 2003, are presented following the rejections as they pertain to the prior art as applied herein.

5. Claims 11, 12 and 14-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al. in view of US 5,763,416 (Bonadio et al., of record) and US 6,048,964 (Lee et al., of record).

6. Claims 11, 12, 14-17 and 19-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al. in view of US 5,763,416 (Bonadio et al.) and US 6,048,964 (Lee et al.) as applied to claims 11, 12 and 14-16 above, and further in view of US 6,291,206 (Wozney et al.).

7. Claims 11, 12, 14-17 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,763,416 (Bonadio et al.) in view of US 6,048,964 (Lee et al.) and Ahrens et al., further in view of US 6,291,206 (Wozney et al.), and further in view of US 5,700,774 (Hattersley et al.)

New Grounds of Rejection

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 11, 12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al. in view of US 5,763,416 (Bonadio et al., of record) and US 6,048,964 (Lee et al., of record).

The claims are drawn to a method for producing cells for implantation at a site of a bone infirmity in a human by transforming a cultured human progenitor cell or a bone marrow stromal cell with a DNA encoding bone morphogenesis protein 2 (BMP-2), then culturing the transformed cell. The cells may be pluripotent progenitor stem cells, a cell line, or a primary cell (claims 12, 14 and 16). The cell may contain an endogenous bone morphogenesis receptor (claim 15).

Ahrens et al. teach at the abstract and materials and methods, the in-vitro transformation of a pluripotent stem cell with DNA encoding BMP-2 protein to study BMP-induced osteogenesis *in vitro*. Ahrens et al. discuss the use of the transformed stem cells in treatment of a bone infirmity (see the introduction and page 879).

Ahrens et al. do not teach the transformation of a human progenitor cell with BMP-2, nor the specific use of BMP-2 transformed cells to treat a bone infirmity.

Bonadio et al. teach at columns 3-9 a method for producing cells for implantation at a site of a bone infirmity in a human (see especially column 5, lines 1-18) by transforming a cultured human progenitor cell or a bone marrow stromal cell with a DNA encoding bone morphogenesis protein 2 (BMP-2) (column 6, line 63-column 7, line 29), then implanting the transformed cell into a site of a bone infirmity. The cells may be pluripotent progenitor stem cells, a cell line, or a

primary cell (see column 4, lines 32-67). Bonadio et al. discuss the affect of BMP on bone formation, and recite the interaction of cells which are "responsive" to BMP's, as well as the intercellular "communication" of cells via bioactive BMP molecules. The need for BMP receptors in "responsive" cells is therefore implied. Bonadio et al. specifically teach the desirability of cotransferring BMP encoding genes and growth factor receptor genes or genes encoding parathyroid hormone (PTH) or PTH receptor protein (column 6 and column 8, line 56-column 9, line 3) into cells for treatment of a bone infirmity.

Lee et al. teach at the claims, the use of BMP-2 to treat a bone infirmity by directly introducing the protein into the site of the bone infirmity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of transforming a pluripotent stem cell *in vitro* with a DNA encoding BMP-2 protein as taught by Ahrens et al. to produce a BMP-2 transformed human mesenchymal progenitor cell *ex-vivo* which may then be introduced into a site of bone infirmity to treat a bone tissue of skeletal defect as taught by Bonadio et al., where Lee et al. teach the usefulness of treating a site of bone infirmity with recombinant BMP-2 protein, to produce the instant claimed method because Ahrens et al. teach the practicality and feasibility of transforming a pluripotent stem cell with a DNA encoding BMP-2 *in vitro*, where Ahrens et al. teach the usefulness of the transformed pluripotent stem cell in a method of treating a site of a bone infirmity, and because Lee et al. teach the practicality and feasibility of treating a bone infirmity by introducing recombinant BMP-2 protein to a site of a bone infirmity. Bonadio et al. specifically teach the

desirability of delivery of a pluripotent stem cell transformed *ex-vivo* with DNA encoding BMP-2 protein to a site of a bone infirmity in a method of treatment of the bone infirmity by inducing osteogenesis at the site of the bone infirmity. Ahrens et al. teach that the transformation of cells with DNA encoding BMP-2 can be done, and Lee et al. teach that delivery of recombinant BMP-2 to cells at a site of a bone infirmity will induce bone regeneration. Therefore, it would have been obvious to one of ordinary skill in the art that the combination of the teachings of Ahrens et al. and Lee et al. provide the reasonable assurance that the method of ex-vivo implanting of the pluripotent transformed cells as taught by Bonadio et al. would be successful for the expected benefit of treating a bone infirmity by regenerating bone tissue.

Response to Arguments

10. Arguments presented in Paper No. 30, filed March 6, 2003, page 3, assert that since Bonadio et al. used direct gene transfer to a site of bone infirmity, that the teachings of Bonadio et al. was not predictive of success of *ex-vivo* use of cells for implantation for bone repair and regeneration. It is asserted that there is no credible support, such as experimental evidence, for the rejection of the claimed subject matter as obvious.

The argument is not found convincing because the claims are drawn to a method for producing cells for implantation. The argument is directed to a method of treatment. Therefore, the limitations of the instant claims are not commensurate with the scope of the argument presented in Paper No. 30.

Bonadio et al. teach the desirability of producing cells transformed by DNA encoding BMP-2 protein for implantation at a site of bone infirmity. Ahrens et al. teach the feasibility and practicality of transforming pluripotent stem cells with DNA encoding BMP-2 protein. Lee et al. teach that the delivery of BMP-2 protein to a site of bone infirmity will induce bone regeneration. Therefore, the combined teachings of Bonadio et al., Ahrens et al. and Lee et al. provide credible support and make obvious the method for producing cells transformed with DNA encoding BMP-2 for implantation to a site of bone infirmity.

11. Arguments presented in Paper No. 30, pages 3-4 assert that the Declaration submitted by Dr. Dan Gazit, Paper No. 29, filed March 6, 2003, demonstrates that one of ordinary skill in the art would not have had a reasonable expectation of success based on *in-vivo* methods as taught by Bonadio et al., and that *ex-vivo* engineered cells showed an unexpected efficiency of functional bone regeneration.

As demonstrated by Ahrens et al., the transformation of pluripotent stem cells with DNA encoding BMP-2 is completely within the realm of reasonable expectation of success. As recited by Bonadio et al. at column 5, lines 1-18, ex-vivo protocols for implantation of transformed cells into animals for effecting bone repair are well known to those of ordinary skill in the art. Therefore, the argument is not found convincing.

Regarding the assertion that *ex-vivo* engineered cells showed an unexpected efficiency of functional bone regeneration, these limitations are not in the claims. Therefore, the argument is moot.

Further regarding the assertion that the method of treating a bone infirmity by implanting cells which have been transformed *ex-vivo* produced unexpected results. It is noted that the two cited references of Gazit et al. and Moutsatsos et al. do not provide unexpected results for the method of implanting cells which have been transformed *ex-vivo* as taught in Bonadio et al. The methods of Gazit et al. and Moutsatsos et al. are essentially the same as the method taught by Bonadio et al. The assertion of unexpected results is directed to a comparison of results of *in-vivo* introduction of the DNA to stem cells versus *ex-vivo* introduction of the DNA to stem cells. Since the teachings of Bonadio et al. make obvious the method of implanting cells which have been transformed *ex-vivo*, there is no unexpected result. Therefore, the argument is moot.

12. Claims 11, 12, 14-17 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al. in view of US 5,763,416 (Bonadio et al.) and US 6,048,964 (Lee et al.) as applied to claims 11, 12 and 14-16 above, and further in view of US 6,291,206 (Wozney et al.).

The claims are drawn to the invention as described above, and where the cells are transformed with a DNA encoding BMP-2 protein and a DNA encoding a bone morphogenesis protein receptor.

Ahrens et al., Bonadio et al. and Lee et al. teach the invention as described above. Bonadio et al. and Lee et al. discuss the affect of BMP on bone formation, and recite the interaction of cells which are "responsive" to BMP's, as well as the intercellular

"communication" of cells via bioactive BMP molecules. The need for BMP receptors in "responsive" cells is therefore implied. Bonadio et al. specifically teach the desirability of cotransferring BMP encoding genes and growth factor receptor genes or genes encoding parathyroid hormone (PTH) or PTH receptor protein (column 6 and column 8, line 56-column 9, line 3) into cells for treatment of a bone infirmity.

Ahrens et al., Bonadio et al. and Lee et al. do not teach the cells are transformed with a DNA encoding BMP-2 protein and a DNA encoding a bone morphogenesis protein receptor.

Wozney et al. teach the bone morphogenesis receptor protein which responds to BMP-2 protein. Wozney et al. teach at column 8, lines 9-22 that it is desirable to transform cells with DNA molecules which encode the BMP receptor protein to increase the responsiveness of the cell to the BMP protein, by increased binding of the BMP protein to the cell, which is desirable to accelerate the effects of the BMP proteins, such as osteoinductive promotion of bone growth.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the cells transformed with DNA encoding BMP-2 protein of Bonadio et al. with the cells transformed with bone morphogenic protein receptor as taught by Wozney et al. for the expected benefit of increasing the responsiveness of the cell to the BMP protein, by increased binding of the BMP protein to the cell, which is desirable to accelerate the effects of the BMP proteins such as osteoinductive promotion of bone growth. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bonadio et al., Lee et al., Ahrens et al. and

Wozney et al. who demonstrate the transformation of cells with DNA encoding BMP proteins and BMP receptor proteins.

13. Claims 11, 12, 14-17 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al. in view of US 5,763,416 (Bonadio et al.) and US 6,048,964 (Lee et al.) and Wozney et al. as applied to claims 11, 12, 14-17 and 19-22 above, and further in view of US 5,700,774 (Hattersley et al., of record).

The claims are drawn to the invention as described above, and where the cells also express a parathyroid hormone (PTH) protein and a parathyroid hormone (PTH) protein receptor.

Ahrens et al., Bonadio et al. and Lee et al. and Wozney et al. teach the invention as described above. Bonadio et al. discuss the affect of BMP on bone formation, and recite the interaction of cells which are "responsive" to BMP's, as well as the intercellular "communication" of cells via bioactive BMP molecules. The need for BMP receptors in "responsive" cells is therefore implied. Bonadio et al. specifically teach the desirability of cotransferring BMP encoding genes and growth factor receptor genes or genes encoding parathyroid hormone (PTH) or PTH receptor protein (column 6 and column 8, line 56-column 9, line 3) into cells for treatment of a bone infirmity.

Ahrens et al., Bonadio et al. and Lee et al. and Wozney et al. do not teach that the cells also express a parathyroid hormone (PTH) protein and a parathyroid hormone (PTH) protein receptor.

Hattersley et al. teach (see especially columns 1 and 2) the use of PTH and PTH receptor in cells in need of treatment with BMP-2, where the affected bone-generating target cells are known to express PTH receptor. PTH is also useful to enrich, and enhance stem cell growth , survival and differentiation (see column 5, lines 15-47).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the cells transformed with DNA encoding BMP-2 protein and BMP receptor protein, and which may also express PTH protein, as taught by Bonadio et al., Lee et al., Ahrens et al. and Wozney et al. with the cells in need of treatment with BMP-2 which also express the PTH and PTH receptor proteins as taught by Hattersley et al. for the expected benefit of enriching, and enhancing stem cell growth , survival and differentiation. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bonadio et al., Lee et al., Ahrens et al., Wozney et al. and Hattersley et al. who demonstrate the transformation of cells with DNA encoding BMP proteins and BMP receptor proteins and where the cells also express PTH and PTH receptor protein.

Conclusion

14. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or

applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
May 12, 2003

REMY YUCEL, PH.D
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